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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/505,308	ESHLEMAN ET AL.	
	Examiner	Art Unit	
	TERRA C. GIBBS	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2008 and 11 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,15,41-43,45 and 59-70* is/are pending in the application.

4a) Of the above claim(s) *59-66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,15,41-43,45 and 67-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 August 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *March 4, 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Election filed March 24, 2008 and Applicant's Amendment filed July 11, 2008.

Claims 2-4 and 44 have been canceled. New claims 67-70 are acknowledged.

Claims 1, 5, 15, 41, 45, and 63 have been amended.

Claims 1, 5, 15, 41-43, 45, and 59-70 are pending in the instant application.

Response to Amendment

Applicant's Amendment filed July 11, 2008 is acknowledged. It is noted that the instant application is fully compliant with 37 CFR 1.121(c).

Election/Restrictions

Applicant's election of Group I, claims 1-5, 15, and 41-45 in the reply filed on March 24, 2008 is acknowledged. Applicant's further election of the species of mammalian from claim 42 and bacteria from claim 43 is also acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Accordingly, claims 59-66 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely made the restriction (election) requirement in the reply filed on March 24, 2008. As discussed *supra*, because Applicant did not point

out the supposed errors in the restriction requirement, the election has been treated as an election without traverse.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1, 5, 15, 41-43, 45, and 67-70 have been examined on the merits.

Information Disclosure Statement

Applicant's information disclosure statement submitted March 4, 2005 is acknowledged. The submission is in compliance with the provisions of 37 CRF 1.97. Accordingly, the information disclosure statement has been considered by the Examiner and a signed copy is enclosed herewith.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because the second invention has made non-initialed and/or non-dated alterations to the oath or declaration. See 37 CFR 1.52(c).

Drawings

The drawings filed on August 20, 2004 are acknowledged. The drawings are objected to because it appears that some of the Figures are color photographs, where only black and white Figures have been submitted. For example, Figure 1 refers to

"blue" and "red"; Figures 2A-D refers to "orange"; Figures 6A-C refers to "red"; and Figures 7A-F refers to "orange". Applicant is reminded that photographs and color drawings are not accepted unless a petition filed under 37 CFR 1.84(a)(2) is granted. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and, unless already present, an amendment to include the following language as the first paragraph of the brief description of the drawings section of the specification:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings and black and white photographs have been satisfied. See 37 CFR 1.84(b)(2).

Nucleotide Sequence Disclosures

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. §1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §1.821-1.825 for the reason(s) set forth below. The disclosure contains sequences which fall under the purview of 37 CFR 1.821 through 1.825 as requiring SEQ ID NOs., but which are not so identified. For example, see page 74, lines 9, 10, 26 and 27; page 75, lines 28-31; page 76, lines 8 and 9; and Table 12 at page 85. The above are examples and are not intended to indicate that the Examiner has made an

exhaustive review of the application. Applicant must fully comply with the requirements of 37 C.F.R. §1.821-1.825 in order for any response to this action to be considered fully responsive.

Specification

Applicant's reference to priority in first sentence of the specification is acknowledged. However, the disclosure is objected to because the specification at page 47, lines 2 and 5; page 51, lines 14 and 17; page 59, line 3; and page 63, line 5, contains embedded hyperlinks and/or other forms of browser-executable code that are impermissible and must be deleted. The attempt to incorporate subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP 608.01(p), paragraph I regarding incorporation by reference. Furthermore, if the application should issue and be placed on the Office web page, the URL may be interpreted as a valid HTML code and become a live web link, transferring a user to a commercial web site. Office policy does not permit the Office to link to any commercial site because the Office exercises no control over the organization, views or accuracy of the information contained on these outside sites. Appropriate correction is required. The above are examples and are not intended to indicate that the Examiner has made an exhaustive review of the application. Applicant must delete the embedded hyperlink and/or other form(s) of browser-executable code in order for any response to this action to be considered fully responsive.

Claim Objections

Claim 41 is objected to because of the following informalities: Claim 41 recites the word, "wherein" twice, back-to-back, in lines 5 and 6. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5, 15, 41-43, 45, and 67-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method for inhibiting replication or transcription of a nucleic acid molecule indicative of a disease state, or an *in vitro* method for selectively treating cells comprising an infectious disease organism, the methods comprising targeting the nucleic acid molecule with an oligonucleotide; and binding of the oligonucleotide to the target nucleic acid molecule; wherein the oligonucleotide comprises a backbone nucleic aid sequence, and two arm nucleic acid sequence, and wherein the backbone nucleic acid sequence is complementary to one stand of the target nucleic acid molecule and the arms are complementary to the other strand of the target nucleic acid molecule, thereby inhibiting transcription of the target nucleic acid molecule, does not reasonably provide enablement for an *in vivo* method for inhibiting replication or transcription of a nucleic acid molecule indicative of a disease state, or an *in vivo* method for selectively treating

cells comprising an infectious disease organism, the methods comprising targeting the nucleic acid molecule with an oligonucleotide; and binding of the oligonucleotide to the target nucleic acid molecule; wherein the oligonucleotide comprises a backbone nucleic aid sequence, and two arm nucleic acid sequence, and wherein the backbone nucleic acid sequence is complementary to one stand of the target nucleic acid molecule and the arms are complementary to the other strand of the target nucleic acid molecule, thereby inhibiting transcription of the target nucleic acid molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This is a scope enablement rejection.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The instant claims are drawn to a method for inhibiting replication or transcription of a nucleic acid molecule indicative of a disease state, or a method for selectively treating cells comprising an infectious disease organism, the methods comprising

targeting the nucleic acid molecule with an oligonucleotide; and binding of the oligonucleotide to the target nucleic acid molecule; wherein the oligonucleotide comprises a backbone nucleic aid sequence, and two arm nucleic acid sequence, and wherein the backbone nucleic acid sequence is complementary to one stand of the target nucleic acid molecule and the arms are complementary to the other strand of the target nucleic acid molecule, thereby inhibiting transcription of the target nucleic acid molecule. The broadness of the methods recited in the claims implies *in vivo* applicability for enablement purposes. In fact, the instant specification at page 4, first paragraph discloses:

> "[I]n a most preferred embodiment, the locked complex inhibits replication of the nucleic acid sequence and/or the locked complex inhibits transcription *in vitro* or *in vivo*".

The nature of the invention, therefore, requires the knowledge of using oligonucleotide molecules that can be delivered to cells in a subject (*in vivo*) such that transcription of the target nucleic acid is inhibited.

The amount of direction or guidance and presence/absence of working examples:

Applicants teach that antigene oligonucleotide treatment of cells results in the lack of the cells to produce clonal growth. It is noted that the cells that Applicants use are human cells in culture and bacterial cells. The specification as filed does not provide sufficient guidance or appropriate examples that would enable a skilled artisan to use the claimed methods in *in vivo* environments. Additionally, a person skilled in the art would recognize that predicting the efficacy of a compound, particularly an oligonucleotide compound, *in vivo,* based solely on its performance *in vitro* is

unpredictable. Thus, although the specification discloses general methodologies of using oligonucleotide compositions *in vivo*, such a disclosure would not be considered enabling since the state of the art of oligonucleotide-mediated gene inhibition in living organisms is highly unpredictable.

The state of the prior art and the predictability or unpredictability of the art:

The claimed invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001). The claims encompass *in vivo* methods for inhibiting replication or transcription of a nucleic acid molecule indicative of a disease state, or *in vivo* methods for selectively treating cells comprising an infectious disease organism, the methods comprising targeting the nucleic acid molecule with an oligonucleotide; and binding of the oligonucleotide to the target nucleic acid molecule; wherein the oligonucleotide comprises a backbone nucleic aid sequence, and two arm nucleic acid sequence, and wherein the backbone nucleic acid sequence is complementary to one stand of the target nucleic acid molecule and the arms are complementary to the other strand of the target nucleic acid molecule, thereby inhibiting transcription of the target nucleic acid molecule. However, the specification only shows that such methods are carried out *in vitro*.

The following references are cited herein to illustrate the state of the art of delivery of oligonucleotide therapeutics into targeted cells *in vivo*:

The instant specification recognizes that antigene oligonucleotides, like other molecular approaches, are designed for the purpose inhibiting transcription of a target

nucleic acid molecule. In fact, the instant specification gives a brief review of existing molecular approaches used to inhibit transcription of a target nucleic acid molecule, including antisense and ribozyme technologies (see Applicant's specification at page 3 and pages 38-40, for example. Similar to Applicant's specification, Scanlon, K. (Current Pharmaceutical Biotechnology, 2004 Vol. 5:415-420) categorize antisense and ribozymes as anti-gene molecules, which use anti-gene technology to illicit gene silencing effects (see Abstract). Scanlon teach the following:

> "[T]here are several issues what need to be surmounted before these anti-gene therapies will become efficacious in the clinic. Primarily, the delivery of an effective pharmacological dose of the anti-gene will be required to impact the specific disease tissue. In addition, the non-specific-specificity and non-antisense activity will require a better understanding if target selectivity is to be demonstrated" (see page 415, first column)
>
> "[D]espite the many successful applications of antisense and ribozymes, the design of such molecules remains largely empiric" (see page 416, second column)
>
> "[K]inetics observed with *in vitro* studies is not always predictive of ribozyme activity *in vivo*" (see page 417, first column)
>
> "[O]ne of the most difficult challenges facing the anti-gene field is efficient transfer system that will stabilize, transduce, and express a transgene in the target tissue... The therapeutic controversy for all anti-gene strategies will always be delivery. The challenge has always been how to deliver the anti-gene" (see page 417, second column)

Regarding the antisense approach in general, a recent (2002) review article by Braasch et al. (Biochemistry, Vol. 41, pages 4503-4510) concludes that major obstacles persist in the art of using nucleic acid therapeutics in treating disease: "[G]ene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology.

Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (see page 4503, paragraphs 1 and 2). Braasch et al. specifically identify 3 factors that contribute to the unpredictable efficacy of using antisense compounds in general: 1) the variable capability of antisense oligonucleotides to access sites within the mRNA to be targeted; 2) problems pertaining to the delivery and uptake of the antisense oligos by cells, with the result that "the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death"; and 3), that "oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism". Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. elaborates, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (see page 4503, paragraphs 1 and 2).

The level of skill in the art:

The relative skill of those in the art is considered to be high, being a graduate student or post-doctoral fellow in a biological science.

The quantity of experimentation necessary:

A review of the instant application fails to find adequate guidance or any disclosure exemplifying the *in vivo* applications as broadly claimed. Although, Applicants clearly recognize the potential of inhibiting transcription of the target nucleic acid molecule *in vivo,* Applicants do not teach the ordinary artisan how to effectively

deliver oligonucleotide therapeutics to target cells *in vivo* to inhibit transcription of the target nucleic acid molecule. No technical guidance or exemplary disclosure is provided regarding the use of the claimed methods for inhibiting transcription of the target nucleic acid molecule in living organisms, using oligonucleotide inhibitors of transcription. As the references above indicate, cell culture results are not readily extrapolated to *in vivo* applications.

Thus, it is maintained that the prior art at the time of Applicant's filing would not enable the use of oligonucleotide therapeutics *in vitro* to support claims directed to the *in vivo* use of oligonucleotides, let alone claims directed to delivering oligonucleotide therapeutics *in vivo*. Accordingly, one skilled in the art, being unable to use the prior art for such guidance, must necessarily find such guidance from the specification. However, one of skill would not find the guidance provided in the specification enough to overcome the unpredictability and challenges of applying results from *in vitro* experiments of inhibition to the *in vivo* methods of inhibiting transcription of the target nucleic acid molecule, as exemplified in the references above.

In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of those oligonucleotides that inhibit transcription of the target nucleic acid molecule that are successfully delivered to target sites in appropriate cells such that transcription of the target nucleic acid molecule is inhibited. Since the specification fails to provide any real guidance for methods of using oligonucleotide therapeutics *in vivo*, and since resolution of the

various complications in regards to targeting a particular gene in a living organism is unpredictable, one of skill in the art would have been unable to practice the invention, commensurate in scope with the claims, without engaging in undue trial and error experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable

over Gibson et al. (Clinical Cancer Research, 2000 Vol. 6:213-222) in view of Escude et al. (Proc. Natl. Acad. Sci., 1999 Vol. 96:10603-10607, Applicant's Reference #1 on the Information Disclosure Statement filed March 4, 2005).

Claim 1 is drawn to a method for inhibiting replication or transcription of a nucleic acid molecule indicative of a disease state, the method comprising targeting the nucleic acid molecule with an oligonucleotide; and binding of the oligonucleotide to the target nucleic acid molecule; wherein the oligonucleotide comprises a backbone nucleic aid sequence, and two arm nucleic acid sequence, and wherein the backbone nucleic acid sequence is complementary to one stand of the target nucleic acid molecule and the arms are complementary to the other strand of the target nucleic acid molecule, thereby inhibiting transcription of the target nucleic acid molecule. Claims 5 and 15 are dependent on claim 1 and include all the limitations of claim 1 with the further limitation wherein the backbone and arms are complementary to a separate stand of a target nucleic acid molecule; and wherein the oligonucleotide has equal or higher specificity and affinity for a target oligonucleotide sequence than the complementary target oligonucleotide sequence. The broadness of the methods recited in the claims implies *in vitro* applicability for art purposes. In fact, the instant specification at page 4, first paragraph discloses:

> "[I]n a most preferred embodiment, the locked complex inhibits replication of the nucleic acid sequence and/or the locked complex inhibits transcription *in vitro* or *in vivo*".

Determining the scope and contents of the prior art

Gibson et al. teach a method for inhibiting transcription in a mammalian cell *in*

vitro comprising administering an anti-bcl-2 ribozyme (see Abstract and Figures 1-3, for example). Gibson et al. teach that bcl-2 is commonly overexpressed in non-oral cancers, such as follicular lymphomas, and this satisfies that bcl-2 is a nucleic acid molecule indicative of a disease state.

Ascertaining the differences between the prior art and the claims at issue

Gibson et al. do not teach an oligonucleotide comprising a backbone nucleic aid sequence, and two arm nucleic acid sequence, and wherein the backbone nucleic acid sequence is complementary to one stand of the target nucleic acid molecule and the arms are complementary to the other strand of the target nucleic acid molecule.

Escude et al. teach a padlock oligonucleotide comprising a backbone nucleic aid sequence, and two arm nucleic acid sequence, and wherein the backbone nucleic acid sequence is complementary to one stand of the target nucleic acid molecule and the arms are complementary to the other strand of the target nucleic acid molecule (see Figure 2, for example). Escude et al. also teach that padlock oligonucleotides are stable in cells and can be used in gene therapy experiments (see Abstract and page 10606, second column, for example).

Resolving the level of ordinary skill in the pertinent art

The level of ordinary skill in the pertinent art is considered to be high, being a graduate student or post-doctoral fellow in a biological science.

Considering objective evidence present in the application indicating obviousness or nonobviousness

It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made to devise a method for inhibiting replication or transcription of a nucleic acid molecule indicative of a disease state, the method comprising targeting the nucleic acid molecule with an oligonucleotide using the teachings of Gibson et al. It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was filed to have the oligonucleotide comprise a backbone nucleic aid sequence, and two arm nucleic acid sequence, and wherein the backbone nucleic acid sequence is complementary to one stand of the target nucleic acid molecule and the arms are complementary to the other strand of the target nucleic acid molecule using the motivation of Escude et al.

One of ordinary skill in the art would have been motivated to devise a method for inhibiting replication or transcription of a nucleic acid molecule indicative of a disease state, the method comprising targeting the nucleic acid molecule with an oligonucleotide since of Gibson et al. taught that such a method could cause cancer cells to lose their malignant behavior. One of ordinary skill in the art would have been motivated to devise a method for inhibiting replication or transcription of a nucleic acid molecule indicative of a disease state, the method comprising targeting the nucleic acid molecule with an oligonucleotide since of Gibson et al. taught that such a method could modify the phenotype of a cancer cell and also cause cancer cells to undergo apoptosis. One of ordinary skill in the art would have been motivated to substitute the anti-bcl-2 ribozyme taught by Gibson et al. with an oligonucleotide comprising a backbone nucleic aid sequence, and two arm nucleic acid sequence, and wherein the backbone nucleic

acid sequence is complementary to one stand of the target nucleic acid molecule and the arms are complementary to the other strand of the target nucleic acid molecule because it is obvious to substitute one functional equivalent for another, particularly when they are to be used for the same purpose. See MPEP 2144.06.

One of ordinary skill in the art would have had a reasonable expectation of devising a method for inhibiting replication or transcription of a nucleic acid molecule indicative of a disease state, the method comprising targeting the nucleic acid molecule with an oligonucleotide since of Gibson et al. taught that the successful use and design of such a method. One of ordinary skill in the art would have had a reasonable expectation of success of substituting the anti-bcl-2 ribozyme taught by Gibson et al. with an oligonucleotide comprising a backbone nucleic aid sequence, and two arm nucleic acid sequence, and wherein the backbone nucleic acid sequence is complementary to one stand of the target nucleic acid molecule and the arms are complementary to the other strand of the target nucleic acid molecule since the substitution of one known element for another would have yielded predictable results at the time of the invention.

Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing.

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Claims 41-43 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. (FEBS Letters, 1999 Vol. 458:151-156), in view of Escude et al. (Proc. Natl. Acad. Sci., 1999 Vol. 96:10603-10607, Applicant's Reference #1 on the

Information Disclosure Statement filed March 4, 2005).

Claim 41 is drawn to a method for selectively treating cells comprising an infectious disease organism, the method comprising targeting the nucleic acid molecule with an oligonucleotide; and binding of the oligonucleotide to the target nucleic acid molecule; wherein the oligonucleotide comprises a backbone nucleic aid sequence, and two arm nucleic acid sequence, and wherein the backbone nucleic acid sequence is complementary to one stand of the target nucleic acid molecule and the arms are complementary to the other strand of the target nucleic acid molecule, thereby inhibiting transcription of the target nucleic acid molecule. Claims 42, 43, and 45 are dependent on claim 41 and include all the limitations of claim 41 with the further limitation wherein the cells are mammalian cells; wherein the cells are infected with a virus, and wherein the oligonucleotide binds to a wild type infectious disease organisms' target gene sequence and any alleles or variants thereof. The broadness of the methods recited in the claims implies *in vitro* applicability for art purposes. In fact, the instant specification at page 4, first paragraph discloses:

> "[I]n a most preferred embodiment, the locked complex inhibits replication of the nucleic acid sequence and/or the locked complex inhibits transcription *in vitro* or *in vivo*".

Determining the scope and contents of the prior art

Zhang et al. teach the *in vitro* cleavage of an anti-HIV-1 DNAzyme, DzV3-9 (see Abstract and Figures 1 and 2, for example). Zhang et al. teach that the anti-HIV1 DNAzyme was administered, detected, and stabilized in mammalian cells (see Figure 3). Zhang et al. also teach that mammalian cells were infected with a virus and virus

replication was inhibited upon administration of DzV3-9 (see Figures 4 and 5).

Ascertaining the differences between the prior art and the claims at issue

Zhang et al. do not teach an oligonucleotide comprising a backbone nucleic aid sequence, and two arm nucleic acid sequence, and wherein the backbone nucleic acid sequence is complementary to one stand of the target nucleic acid molecule and the arms are complementary to the other strand of the target nucleic acid molecule.

Escude et al. teach a padlock oligonucleotide comprising a backbone nucleic aid sequence, and two arm nucleic acid sequence, and wherein the backbone nucleic acid sequence is complementary to one stand of the target nucleic acid molecule and the arms are complementary to the other strand of the target nucleic acid molecule (see Figure 2, for example). Escude et al. also teach that padlock oligonucleotides are stable in cells and can be used in gene therapy experiments (see Abstract and page 10606, second column, for example).

Resolving the level of ordinary skill in the pertinent art

The level of ordinary skill in the pertinent art is considered to be high, being a graduate student or post-doctoral fellow in a biological science.

Considering objective evidence present in the application indicating obviousness or nonobviousness

It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made to devise a method for selectively treating cells comprising an infectious disease organism, the method comprising targeting the nucleic acid molecule with an oligonucleotide using the teachings of Zhang et al. It would have been

prima facie obvious to one of ordinary skill in the art, at the time the invention was filed to have the oligonucleotide comprise a backbone nucleic aid sequence, and two arm nucleic acid sequence, and wherein the backbone nucleic acid sequence is complementary to one stand of the target nucleic acid molecule and the arms are complementary to the other strand of the target nucleic acid molecule using the motivation of Escude et al.

One of ordinary skill in the art would have been motivated to devise a method for selectively treating cells comprising an infectious disease organism, the method comprising targeting the nucleic acid molecule with an oligonucleotide since of Zhang et al. taught that such a method could inhibit viral infection and infection by incoming virus. One of ordinary skill in the art would have been motivated to substitute the anti-HIV-1 DNAzyme taught by Zhang et al. with an oligonucleotide comprising a backbone nucleic aid sequence, and two arm nucleic acid sequence, and wherein the backbone nucleic acid sequence is complementary to one stand of the target nucleic acid molecule and the arms are complementary to the other strand of the target nucleic acid molecule because it is obvious to substitute one functional equivalent for another, particularly when they are to be used for the same purpose. See MPEP 2144.06.

One of ordinary skill in the art would have had a reasonable expectation of devising a method for selectively treating cells comprising an infectious disease organism, the method comprising targeting the nucleic acid molecule with an oligonucleotide since of Zhang et al. taught that the successful use and design of such a method. One of ordinary skill in the art would have had a reasonable expectation of

success of substituting the anti-HIV-1 DNAzyme taught by Zhang et al. with an oligonucleotide comprising a backbone nucleic aid sequence, and two arm nucleic acid sequence, and wherein the backbone nucleic acid sequence is complementary to one stand of the target nucleic acid molecule and the arms are complementary to the other strand of the target nucleic acid molecule since the substitution of one known element for another would have yielded predictable results at the time of the invention.

Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James “Doug” Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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October 24, 2008
/Terra Cotta Gibbs/